Study Protocol and Statistical Analysis Plan

Temporary Autonomic Blockade to Prevent Atrial Fibrillation after Cardiac Surgery

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Study Design

We conducted a randomized, double-blind, placebo-controlled trial in a single cardiothoracic surgery program at two hospitals in a large academic health system. Prior to beginning the trial, we obtained institutional review board approval from Duke University Medical Center, FDA approval for an investigational new drug application, and registered the trial at ClinicalTrials.gov (NCT02498769).

Participants

The trial enrolled adult patients undergoing CABG, valve surgery, or CABG/valve surgery performed via sternotomy using cardiopulmonary bypass. Patients >90 or <50 years of age, those with long-standing persistent AF, prior cardiac surgery, left ventricular ejection fraction <25%, preoperative inotropic support, hepatic dysfunction (AST or ALT > 1.5x upper limit of normal), renal dysfunction (serum creatinine > 2.0 mg/dL), known sensitivity to botulinum toxin, debilitating neuromuscular disease, or those with a history of second-degree or third-degree atrioventricular block were excluded from the study. All patients gave both verbal and written consent to participate in the trial.

Randomization and Masking

Eligible patients were randomly assigned utilizing a computer-generated mixed block size in a 1:1 ratio to receive epicardial injections of either 250 units (5 mL) of onabotulinumtoxinA (Botox™) or an equivalent volume of identical normal saline (placebo injection) equally amongst five identical syringes.

Procedures

The attending cardiac surgeon performed injections immediately after initiation of cardiopulmonary bypass, prior to the primary surgical procedure. Study solution (1mL consisting of 50 units onabotulinumtoxinA or 1mL placebo) was injected using a 27g needle under direct vision into all five epicardial fat pads, including the anterior fat pad, and the fat pads associated with each pulmonary vein. The remainder of perioperative care was managed according to the primary team.

Outcomes

The primary end point of this study was time to >30 seconds of in-hospital POAF as assessed by continuous telemetry during the postoperative hospitalization. Pre-specified secondary end points included the incidence of POAF, and among those developing POAF the duration of first POAF episode, in-hospital burden of POAF (percent of postoperative hospitalization spent in AF), proportion of recurrent (greater than one episode lasting >30s) or prolonged (two days or greater in duration[1]) POAF, and need for POAF treatment (medications administered for rate control, rhythm control, or electrical cardioversions for POAF). Additionally, the ICU and hospital LOS were compared between groups. As an exploratory analysis, we also examined the incidence of

hemodynamically significant new-onset POAF, resulting in rapid ventricular response (heart rate > 100 BPM) and hypotension (systolic blood pressure < 100 mmHg).

Safety end points included the incidence of any adverse event or postoperative complication, the incidence of adverse events prolonging LOS, and postoperative mortality. Additionally, duration of postoperative mechanical ventilation and the incidence of reintubation were compared between groups.

Statistical Analysis

Based on a pilot trial showing a pronounced reduction (30 day relative risk reduction 78%) in POAF after injecting BoNTA into the epicardial fat pads,[2] we anticipated a significant reduction in the risk for POAF with epicardial BoNTA injection in our cohort. Our study sought to include valve surgery patients, which would result in a higher-risk population for POAF. Based upon a two-tailed alpha of 0.05, an estimated POAF incidence of 40% in the control group, and a total sample size of 130 (n=65 in each arm), we prospectively determined 80% power to detect a 40% difference in relative risk (corresponding to a hazard ratio of 0.4) between treatment groups for the primary outcome.

Analyses were based on the intention-to-treat principle in all patients who received epicardial injection (modified intention-to-treat analysis). Patient characteristics were summarized by standard descriptive statistics and were compared between groups using t-tests, Wilcoxon rank sum tests, Chi-square tests, or Fisher exact tests as appropriate. The Kaplan-Meier method was used to construct non-parametric estimates of the distribution of time to first POAF event. Adjustment of treatment effect for baseline factors previously found associated with POAF outcome was accomplished using Cox proportional hazards modeling. The proportional hazards assumption was confirmed via log-log plots, plots of Schoenfeld residuals by time, and testing of a group-time interaction in the model. Secondary analyses were conducted via parametric and non-parametric assessments as appropriate.

Secondary analysis of incidence of POAF was conducted via univariable and adjusted logistic regression with the same baseline characteristics as in the primary outcome model. Heterogeneity of treatment effect was explored in patient subgroups defined by surgery type, POAF risk as assessed by the Multicenter Study of Perioperative Ischemia (McSPI) AFRisk index,[3] preoperative angiotensin converting enzyme inhibitor (ACEi) use, beta-blocker use, diabetes, and congestive heart failure. We studied differences in ICU and hospital LOS via Wilcoxon rank sum tests. In order to characterize severity of POAF between groups, we explored group differences among patients who developed POAF in duration of first POAF, initial ventricular rate, total POAF duration (cumulative duration of all in-hospital POAF), and total POAF burden (percent of postoperative hospital LOS spent in AF) via Wilcoxon rank sum tests. We compared the incidence of recurrent POAF, hemodynamically significant POAF, two or greater days of POAF,[1] and need for treatment for AF via Chi-Square or Fisher exact tests. We investigated differences in the incidence of safety endpoints via Chi-Square or Fisher exact tests, and used a Wilcoxon rank sum test to explore differences in duration of postoperative mechanical ventilation.

Because multiple comparisons of secondary outcomes were performed without post-hoc adjustment of the significance level, these outcomes should be interpreted as

exploratory. All comparisons were 2-tailed and significance was set at $p<0.05$. Analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC). A data safety monitoring board consisting of a cardiothoracic surgeon, cardiothoracic anesthesiologist, cardiac electrophysiologist, and biostatistician examined blinded, aggregate adverse event data at 10%, 25%, and 50% accrual in order to ensure adequate safety of the study.

References

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